Medication-Induced Interstitial Nephritis in the 21st Century

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Interstitial nephritis is an immune mediated form of tubulointerstitial kidney injury that may occur secondary to drugs, autoimmune disease, infections, and hematologic disorders or as a reactive process. Drug-induced acute interstitial nephritis (DI-AIN) occurs in 0.5%-3% of all kidney biopsies and in 5%-27% of biopsies performed for acute kidney injury. Drugs are implicated in 70%-90% of biopsy-proved IN with a prevalence of 50% in less developed to 78% in more developed countries. DI-AIN typically is idiosyncratic because of a delayed hypersensitivity reaction, although some chemotherapeutic agents are permissive for immune upregulation and injure the kidney in a dose-related manner. Antibiotics are the most implicated class of medication in DI-AIN, followed by proton pump inhibitors, nonsteroidal anti-inflammatory agents, and 5-aminosalicylates. Diuretics, allopurinol, phenytoin and other anti-seizure medications, and H2 receptor antagonists are known offenders while chemotherapeutic agents are an under-recognized cause. The symptoms of DI-AIN are variable and often not specific; thus, kidney biopsy is required to make a firm diagnosis. The incidence of DI-AIN appears to be increasing, particularly in the elderly in whom kidney biopsy is underused, and identification of the offending agent may be complicated by polypharmacy. As rapid drug discontinuation may improve prognosis, the possibility of DI-AIN should always be considered in a patient with acute kidney injury.

Key Words: Interstitial nephritis, Medications, Kidney failure

INTRODUCTION

Interstitial nephritis (IN) is an immune mediated form of tubulointerstitial kidney injury that may occur secondary to drugs, autoimmune disease, infections, and hematologic disorders or as a reactive process.[1-6] One of the first described cases of drug-induced acute interstitial nephritis (DI-AIN) was reported in 1946 and caused by sulfonamides, with patients displaying a spectrum of clinical symptoms including allergic reactions.[7] It is now recognized that the clinical presentation of drug-induced AIN is variable, often without the hallmark features of eosinophilia, rash, and fever; these features of AIN and mechanisms and treatment are discussed in detail elsewhere in this journal issue. As the symptoms of IN often are not specific, definitive diagnosis requires kidney biopsy and clinical-pathologic correlation to identify the underlying etiology. Although it is difficult to determine the true incidence of interstitial nephritis, AIN is identified in 0.5%-3% of all kidney biopsies and is the finding in 5%-27% of biopsies performed for acute kidney injury.[1,8,9] Currently, AIN most often is because of drug hypersensitivity or allergic reaction with antibiotics as the leading cause, with a prevalence ranging from 50% in less developed to 78% in more developed countries.[1,8] Despite the regular identification of DI-AIN in kidney biopsies, interstitial nephritis is a rare drug side effect occurring in far less than 1% of treated patients. However, certain medications are associated with increased risk, with AIN identified in up to 17% of patients treated with methicillin. Additionally, the incidence of AIN appears to be increasing, particularly in the elderly, and after withdrawal of the offending agent and/or treatment, baseline kidney function is achieved in only 30%-70% of patients.[9-13]

Therapeutic agents are responsible for 70%-90% of biopsy-proven AIN, and in most cases, the etiology is a delayed hypersensitivity immune reaction driven by antigen-reactive T cells; therefore, the reaction is idiosyncratic, not dose related, and occurs with drug rechallenge.[2,9] Specific mechanisms of drug-induced injury include the drug or a metabolite acting as a hapten after binding to the tubular basement membrane, functioning as a planted antigen after binding to a component of the interstitium or tubular basement membrane, evoking an antibody response with formation of circulating immune complexes which then deposit in the tubulointerstitium or displaying molecular mimicry wherein there is cross-reactivity with a tubular basement membrane or interstitial antigen with a subsequent elicited T-cell immune response.[14] Exceptions to this include some chemotherapeutic agents that are permissive for immune upregulation and injure the kidney in a dose-related manner, and nonsteroidal anti-inflammatory agents in which there may be a typical hypersensitivity reaction and an increase in leukotrienes, which then activate T cells.[15,16]

In drug-induced chronic interstitial nephritis (CIN), the inflammatory reaction often persists with ensuing organization, rather than resolution and resulting tubulointerstitial scarring.[17] This process may begin as quickly as 1 week after the initial inflammatory process with progressive loss of kidney function and few specific clinical findings. CIN may occur in those with ongoing medication use and associated inflammation, whereas some medications such as 5-aminosalicylic acid are associated with inflammation that may persist for months or years after drug discontinuation; in both cases, the inflammation likely injures tubular epithelial cells and/or pericytes with subsequent fibrosis. There are drugs, such as lithium, that incite a fibrotic

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tubulointerstitial response without preceding acute parenchymal injury. Furthermore, in patients with pre-existing kidney disease, there is increased risk for DI-IN to progress to kidney failure. Below are the morphologic features of drug-induced interstitial nephritis, and the common and newer medications associated with this lesion are listed in Table 1.

MORPHOLOGY OF INTERSTITIAL NEPHRITIS

Acute Interstitial Nephritis

AIN is a nonspecific finding, in that the features typically do not identify the underlying etiology. The histologic hallmarks of AIN are focal to diffuse interstitial edema and an inflammatory infiltrate which is composed of lymphocytes, predominantly T cells (Fig 1). There are variable numbers of macrophages and plasma cells observed in the majority of cases, whereas the presence of eosinophils is not required and is often minimal or absent with many current medications. Neutrophils may be present, typically focally and in small numbers, and have been associated with a better prognosis after steroid therapy.[18] Inflammation prominent at the corticomedullary junction is considered to be more indicative of a drug-induced reaction. Tubules show acute epithelial cell injury, and with more severe nephritis, there is tubular inflammation; this finding often is designated acute tubulointerstitial nephritis, a term coined in 1960s with the acknowledgment of tubular injury in concert with interstitial inflammation.[19] Granulomas are identified in 0.5% to 0.9% of kidney biopsies, and of these, 17.5%-45% have been determined to be part of a drug-induced IN.[20-22] In this setting, it is necessary to exclude infection and autoimmune diseases, such as sarcoidosis and tubulointerstitial nephritis-uveitis syndrome. When there are severe tubular inflammation and epithelial cell injury, granulomas also may form as a reaction to tubular rupture and extra-tubular Tamm-Horsfall protein. Immunofluorescence and electron microscopy are helpful only by excluding other potential causes of interstitial nephritis, such as immune complex deposition or anti-tubular basement membrane antibody nephritis.

CLINICAL SUMMARY

- Interstitial nephritis most often is caused by antibiotics, nonsteroidal anti-inflammatory agents, and proton pump inhibitors.
- Many classes of drugs may induce interstitial nephritis including newer chemotherapeutic agents, anticoagulants, antidepressants, and others.
- The incidence of drug-induced interstitial nephritis is increasing, particularly in the elderly.
- Kidney biopsy is required to make a definitive diagnosis of interstitial nephritis.
- Kidney biopsy often is not performed in cancer patients, resulting in missed opportunities to treat and reverse interstitial nephritis.

Chronic Interstitial Nephritis

Ongoing kidney parenchymal inflammatory changes can begin to undergo scarring within a week to 10 days from initiation of the acute injury. Continued use of the offending medication or extensive acute injury that does not respond quickly to drug withdrawal or steroid treatment may result in chronic injury characterized by interstitial fibrosis with tubular atrophy, a variable extent of inflammation in the fibrotic areas and frequently inflammation in atrophied tubules (Fig 1). The inflammation is composed of lymphocytes, macrophages, and plasma cells to differing extents, with variable numbers of eosinophils as in acute interstitial nephritis. The inflammation is restricted to the areas of scarring and does not involve the adjacent preserved tubulointerstitium in cases of pure CIN. However, when there is ongoing administration of the offending drug, AIN and CIN may occur simultaneously with both edema and fibrosis, and inflammatory cells in the scarred and preserved parenchyma. CIN may have a granulomatous component and the same caveats apply as noted earlier. The extent of tubulointerstitial fibrosis is closely linked to kidney function and is an important predictor of kidney functional recovery.[23,24]

MEDICATIONS INDUCING INTERSTITIAL NEPHRITIS

Medications are the etiology of AIN in 70%-90% of biopsy-proven cases; antibiotics, followed by proton pump inhibitors (PPIs) and nonsteroidal anti-inflammatory agents (NSAIDs), are the most common offenders, although theoretically, any drug can induce IN.[1,8] In up to 15% of AIN cases studied at the Mayo Clinic, the cause was felt to be multidrug.[1] As noted earlier, granulomas are not rare in drug-induced IN and are associated with antibiotics, analgesics, including NSAIDs, PPIs, and a variety of other medications. Therefore, drugs should always be a consideration when granulomas are found in the renal tubulointerstitium.

Antibiotics

Kidney inflammation with hypersensitivity drug reactions including eosinophilia, rash, and fever was first recognized in the 1940s associated with sulfonamides.[7] This ushered in the awareness of drug-induced AIN and subsequently penicillin and its derivatives were identified as causes of AIN, a harbinger of the long list of antibiotics subsequently associated with kidney inflammation and that encompasses virtually all classes of antimicrobial agents[2,25] (Table 1). There are few recent studies specifically addressing the incidence of antimicrobials as the cause of biopsy-proved AIN; this class of drugs was identified as the etiology in 35% of such cases in Scotland, and in 49% from the Mayo Clinic, and are considered the leading cause of DI-AIN.[1,13] The mechanism of AIN secondary to antibiotics is almost universally an idiosyncratic